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OrCel™

(Bilayered Cellular Matrix)

Instructions for Use

For Managing Donor Sites in Burn Patients

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Instructions for Use

CAUTION: Federal Law restricts this device to sale by or on the order of a physician.

1. INDICATIONS FOR USE

OrCel™ is indicated for the treatment of fresh, clean split thickness donor site wounds in burn patients.

2. PRODUCT DESCRIPTION

OrCel™ is a bilayered cellular matrix in which normal human allogeneic skin cells (epidermal keratinocytes and dermal fibroblasts) are cultured in two separate layers into a Type I bovine collagen sponge. Donor dermal fibroblasts are cultured on and within the porous sponge side of the collagen matrix while keratinocytes, from the same donor, are cultured on the coated, non-porous side of the collagen matrix. OrCel™ serves as an absorbable biocompatible matrix that provides a favorable environment for host cell migration and has been shown to contain the following cell-expressed cytokines and growth factors: FGF-1 (bFGF), NGF, GM-CSF, IL-1α, IL-1β, IL-6, HGF, KGF-1 (FGF-7), M-CSF, PDGF-AB, TGF-α, TGF-β1, TGF-β2, and VEGF. OrCel™ is not intended to be a human skin replacement and does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels or hair follicles. DNA analysis performed on two OrCel™ -treated donor site patient tissue samples showed no trace of allogeneic cell DNA after two or three weeks respectively.

OrCel™ is manufactured under aseptic conditions from human neonatal foreskin tissue. The donor's mother is tested and found to be negative for syphilis and for human viruses, including CMV, HSV I & II, HTLV I & II, Hepatitis B&C, HIV 1&2, EBV and HHV-6. The donor's fibroblast and keratinocyte cells are tested and found to be negative for viruses and retroviruses (including HTLV I&II, Hepatitis B, HIV 1&2, EBV, and HHV-6), bacteria, fungi, yeast, mycoplasma, and tumorigenicity. The donor cells **are** tested and **are** found to be normal human cells using karyology, isoenzyme, growth and morphological analyses. Prior to cell seeding, the matrix is cross-linked and then coated on one side with a thin gel layer prepared from acid-soluble collagen. The final product is tested for morphology, cell density, cell viability, sterility, mycoplasma, and physical container integrity. All animal derived reagents are tested for: viruses, bacteria, fungi, yeast, and mycoplasma before use, and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE). The device measures approximately 6 cm x 6 cm (minimally 36 cm^2).

3. CONTRAINDICATIONS

- OrCel™ is contraindicated for use on clinically infected wounds.
- OrCel™ is contraindicated in patients with known allergies to bovine collagen.

4. WARNINGS

OrCel™ is not indicated for the treatment of burns and is not intended to be a substitute for autograft.

Allergic reactions to bovine collagen have been reported in the literature. Since bovine collagen is a component of OrCel™, discontinue product use if a patient shows evidence of an immune reaction.

5. PRECAUTIONS

Caution: The safety and effectiveness of Orcel™ has not been studied on patients under12 months of age, in pregnant or lactating females, in patients previously treated with immunosuppressive agents, radiation or chemotherapy in the three months prior to treatment, in patients with a history of insulin dependent diabetes with a HbA1C>10%, or in septic patients.

Caution: OrCel™ may contain trace amounts of penicillin, streptomycin, gentamicin, and fungizone (amphotericin B) used during cell processing. Avoid the use of this product in patients known to be allergic to these materials.

Caution: Allergic reactions to the components (see Section 8) of the shipping medium have been reported in the literature. Patients should notify their physician of any symptoms of an allergic reaction. In clinical studies evaluating over 214 patients, no allergic reactions to the shipping medium were reported.

Caution: OrCel™ should be stored in its shipping container until ready for use.

Caution: Do not use cytotoxic agents with OrCel™. Device exposure to mafenide acetate, silver sulfadiazine, polymyxin/nystatin, Povidone-iodine solution or Dakin's Solution may also reduce OrCel™'s viability.

Caution: If clinical signs of infection (such as: pain, edema, erythema, drainage, odor, warmth, and/or unexplained fever) are present or develop, do not apply OrCel™ until the infection is adequately treated and eradicated. All infections should be evaluated and treated according to standard clinical practice.

Caution: OrCel™ should be handled using aseptic technique and placed on a fresh, clean donor site wound within 30 minutes of removing sterile tray from sealed pouch.

Caution: The safety and effectiveness of OrCel™ has not been evaluated in burn patients with split thickness donor sites larger than 288 cm^2 (8 pieces of OrCel™). On average patients received 2 pieces of OrCel™ to cover their donor sites.

Caution: The duration of OrCel™ cells on donor site wounds is not known.

Caution: The safety of OrCel™ in the donor site patient population has not been established beyond one year. *In vitro, in vivo*, and clinical testing to date, have not revealed a tumorigenic potential of the OrCel™ cells.

Caution: The potential for a humoral or cellular immune response to the allogeneic cells in OrCel™ remains unknown. In 214 patients treated with OrCel™ the clinical trial investigators have reported no clinical evidence of immune reaction to the product.

Caution: The effects of anabolic steroids on wound closure are unknown.

Caution: **DO NOT OPEN AND DO NOT USE** OrCel™ after the expiration date (see Section 8).

Caution: **DO NOT USE** OrCel™ if sterile package is opened or damaged.

Caution: **DO NOT REUSE, FREEZE, REFRIGERATE, OR STERILIZE.**

6. ADVERSE EVENTS

In two within-patient studies comparing OrCel™ with a control semi-permeable biological wound dressing, a total of 90 patients were evaluated for safety after treatment of split thickness donor sites in burn patients. Table 1 lists all reported adverse events related to the treated donor sites. Table 2 lists all systemic adverse events with a frequency greater than two events. Because all patients received both OrCel™ and control treatments, attributing causality for systemic adverse events to a specific treatment was not feasible.

Table 1: Adverse Events Related to the Treated Donor Sites

Adverse Events	Donor Site	
	OrCel™	Control
Pain	6 (6.7%)	6 (6.7%)
Pruritus	4 (4.4%)	5 (5.6%)
Itching	2 (2.2%)	2 (2.2%)
Infection	1 (1.1%)	2 (2.2%)
Rash Pustular	1 (1.1%)	----
Tenderness to palpation	1 (1.1%)	----
Blisters	----	1 (1.1%)
Bullous Eruption	----	1 (1.1%)
Conversion to full thickness wound	----	1 (1.1%)
Excision & regrafting of donor site	----	1 (1.1%)

Table 2: Systemic Adverse Events With a Frequency >2 Occurrences

Adverse Events	Frequency
Constipation	19 (21.1%)
Anaemia	13 (14.4%)
Insomnia	12 (13.3%)
Fever	11 (12.2%)
Vomiting	10 (11.1%)
Infection	9 (10.0%)
Nausea	9 (10.0%)
Pharyngitis	8 (8.9%)
Pruritis	8 (8.9%)
Hyperglycaemia	7 (7.7%)
Agitation	6 (6.7%)
Sepsis	6 (6.7%)

Adverse Events	Frequency
Anxiety	5 (5.6%)
Atelectasis	5 (5.6%)
Hypernatraemia	5 (5.6%)
Relaxation Of Scar	5 (5.6%)
Thrombocythaemia	5 (5.6%)
Diarrhea	4 (4.4%)
Dyspnea	4 (4.4%)
Dyspepsia	4 (4.4%)
Rehabilitation NEC	4 (4.4%)
Thrombocytopenia	4 (4.4%)
Death	4 (4.4%)
Depression	3 (3.3%)
Hypokalaemia	3 (3.3%)
Hypotension	3 (3.3%)
Urinary Tract Infection	3 (3.3%)
Edema	3 (3.3%)
Other Local Destruc Skin	3 (3.3%)
Pulmonary Infiltration	3 (3.3%)
Scar	3 (3.3%)
Skin Malformation	3 (3.3%)
Pneumothorax	3 (3.3%)

A total of four patients died, three during the pivotal study and one during the pilot study. Two patients had Adult Respiratory Distress Syndrome (ARDS). Both patients had predisposing respiratory conditions in their medical conditions prior to study start. The third patient had bacterial sepsis secondary to burn injuries resulting in death. The fourth patient had septic shock and multi-system organ failure secondary to burn injuries resulting in death.

7. CLINICAL EXPERIENCE

A pilot and pivotal study were conducted in the management of donor sites in patients requiring split thickness skin autografting for the management of burn injuries. Both studies were prospective, evaluator-masked, randomized and controlled. They were matched-pair design (i.e., each patient had two designated donor sites of equivalent surface area) and donor sites were randomized allowing each patient to receive a single application of OrCel™ and a control semi-permeable biological wound dressing.

The pilot study was a single center trial within patient control and included eight patients. The objective was to examine preliminary safety data and evaluate performance of OrCel™ in management of split thickness donor sites in burn patients. Patients in this study were 10 years of age and older and had burns involving at least 10% but not greater than 60% of total body surface area. The total donor surface area comprised a minimum of 72 cm^2 and a maximum of 144 cm^2.

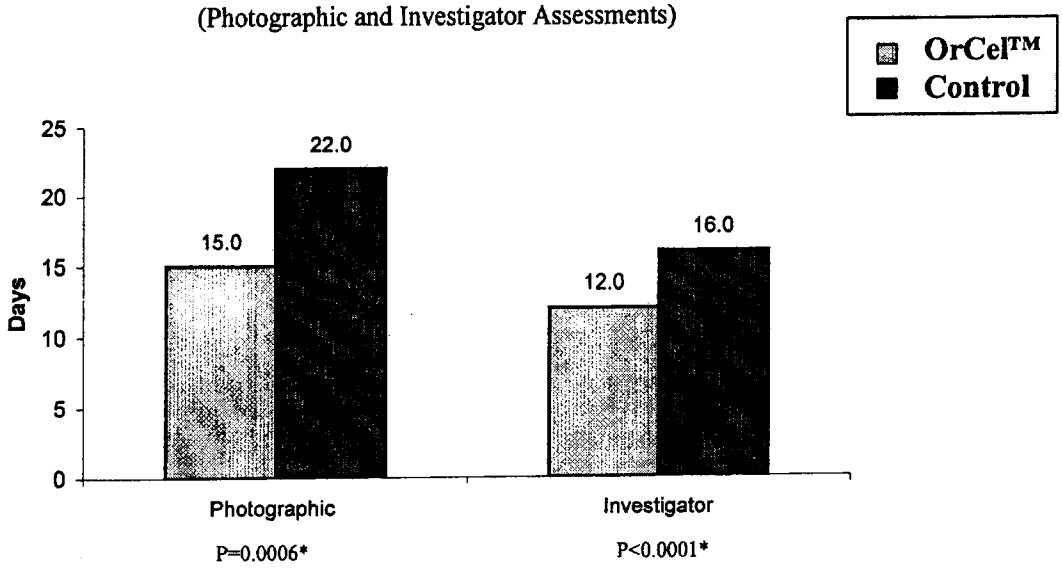
The primary outcome measure was the time to complete wound closure, measured in days to 100% re-epithelialization assessed by computerized planimetric analysis. Kaplan-Meier estimates of the percent of healing from both computerized planimetric analysis and the investigators' assessments showed that at least 50% of the eight patients were healed by Day 12 with OrCel™ treatment and by day 25 with the control dressing.

The pivotal study was a multi-center study evaluating the safety and effectiveness of OrCel™ in the treatment of split thickness donor sites burn patients. The main criteria for inclusion in the pivotal study specified patients 1 year of age and older, and the presence of burns involving at least 10% but not greater than 80% of total body surface area including burns of thermal (flame, scald and contact), chemical and friction etiology. Donor sites treated had to be virgin areas and could be located on anterior or posterior non-articulated surface areas. Total (investigational treatment and control) donor surface could be between 72 cm^2 to 360 cm^2 in patients greater than 3 years of age and 36 cm^2 to 180 cm^2 in patients less than 3 years of age. Split thickness autografts were harvested between 0.006-0.014 inch depth.

The primary efficacy outcome was time to 100% wound closure (complete re-epithelialization) as assessed by blinded photographic analysis. Secondary outcome variables also assessed time to 100% wound closure by investigator assessment and computerized planimetric analysis. One hundred percent wound closure was defined as the presence of a dry, opalescent-pink external surface representing the newly formed cornified layer of the epidermis which in the clinician's assessment would no longer require a dressing or protective covering. Patients were assessed at Day 0, Day 7, 14, 21, 28, Week 12, and Week 24. After Day 7, patients were assessed every 48 hours until 100% wound closure was documented at both treatment sites.

The study was conducted at 12 clinical sites and included 82 patients. The following graph illustrates the Median days to 100% wound closure based on photographic and investigator assessments (Figure 1).

Figure 1. Median Days to 100% Wound Closure
N=82
(Photographic and Investigator Assessments)



*Log-Rank test of the difference between treatment healing times, stratified by patient

The median times to 100% wound healing as assessed by photographic and investigator evaluations were significantly shorter ($p<0.0006$) for OrCel™ treated sites compared to the control dressing. The median days to closure for OrCel™ treated wounds was seven days faster as assessed by photography and 4 days faster as assessed by the investigators.

Only 3 OrCel™ treated donor sites were recropped. The number of patients was insufficient to evaluate the results of recropping the treated study sites or the re-healing of recropped site.

Subpopulations Analysis

The impact of baseline characteristic on 100% wound closure was analyzed for different patient characteristics and is reported below as Table 3. The impact of a mild anabolic steroid[1] is included in this analysis because it was administered to a segment of the trial population (N=30).

Table 3: Median Days to 100% Wound Closure

	N	Median Days (Photography)		Median Days (Physician Assessment)	
		OrCel™	Control	OrCel™	Control
Male	63	12.0	16.0	12.0	16.0
Female	19	12.0	19.0	12.0	21.0
<15 years	22	14.0	14.0	12.0	14.0
15-65 years	57	17.0	29.0	13.0	17.0
>65 years	3	14.0	29.0	16.0	29.0
White	44	15.0	20.0	12.0	16.0
Black	20	14.0	21.0	14.0	21.0
Other	18	17.5	22.0	12.0	15.5
TBSA <20%	21	14.0	14.0	11.0	14.0
TBSA 20-40%	47	17.0	29.0	12.0	16.0
TBSA >40%	14	21.0	32.0	16.0	25.0
Donor Area ≤45cm	20	14.0	21.0	12.0	17.5
Donor Area >45cm	62	17.0	28.0	13.0	16.0
Pts w/ anabolic steroid[1]	30	20.0	32.0	14.0	22.0
Pts w/o anabolic steroid[1]	52	14.0	19.0	12.0	14.5

[1] Indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infection, or severe trauma

Secondary Endpoints

OrCel™ treatment resulted in statistically significant differences in scores at weeks 12 and 24 when compared to the control dressing, as measured by the Vancouver and Hamilton Scar Scales.

Table 4: Scar Outcome as Measured by Vancouver and Hamilton Scar Scales

	Vancouver Scar Scale*			Hamilton Scar Scale**	
	Week 12	Week 24	Week 52	Week 12	Week 24
OrCel™	2.26	2.56	3.10	3.89	2.96
Control	3.07	3.79	3.95	4.95	3.50

* Vancouver Scar Scale is measured from a range of 0 to 15; 0 representing no scarring, 15 representing the most severe scarring.

**Hamilton Scar Scale is measured from a range of 0 to 20; 0 representing no scarring, 20 representing the most severe scarring.

Immune Response

The impact of device application on patients' humoral and cellular immune responses to the allogeneic human cellular components of OrCel™, i.e., keratinocytes and fibroblasts, such as HLA antigens or potential blood group antigens, has not yet been evaluated. In sera drawn from 90 patients treated in the donor site study, 2 patients exhibited elevations from baseline (8-9 Enzyme Immunoassay (EIA) units), 5 patients exhibited an indeterminate response (5-10 EIA units), and 8 patients exhibited a new positive antibody response (10-78 EIA units) to Type I collagen. Investigations with OrCel™, to date, have not revealed any clinical manifestations of product-related immune reactions. In the literature, studies of pretreatment serology show that approximately 8.4% of patients have pre-existing antibovine collagen antibodies.

8. HOW SUPPLIED

A. Package Description

OrCel™ measures approximately 6 cm x 6 cm (minimally 36 cm^2). A non-adherent, mesh is placed on both aspects of the device to protect the cells. One sheet is blue mesh, which covers the fibroblast/dermal side of OrCel™. The other sheet is white mesh, which protects the keratinocyte/epidermal surface of OrCel™. The device is packaged in a plastic tray with protein-free packaging medium containing HEPES buffered DMEM, L-Glutamine and MEM non-essential amino acids to maintain cell viability during storage and shipping.

The plastic tray is sealed within a peelable inner pouch to provide a sterile barrier against moisture and gas. The inner pouch is, in turn, sealed inside a heavier-gauge outer pouch that protects the inner pouch sterile barrier and the product against damage during shipment. The multi-stage packaged product is packed with pre-chilled gel packs and shipped to the destination in a padded and insulated shipping container that maintains a temperature of 11-19° C (for up to 72 hr.).

To maintain cell viability, OrCel™ is aseptically manufactured, but not terminally sterilized. OrCel™ is shipped following a preliminary 48 hour incubation sterility test to confirm the absence of microbial growth. Final (14 day incubation) sterility test results are not available at the time of device application.

B. Storage

1. OrCel™ is to be stored in the original shipping container in which it was received. Do not store in a refrigerator or freezer. The original shipping container maintains the correct storage temperature of 11 to 19°C.

2. Do not remove from original shipping container until ready to use.

C. Package Inspection

1. Visually inspect the OrCel™ clear packaging. The clear packaging should be intact. If the packaging is damaged, the OrCel™ device is not acceptable for patient application.
2. Visually inspect the medium in which the OrCel™ device is transported. The medium should not appear cloudy in color. Any cloudiness of the medium is an indicator that the OrCel™ device is not acceptable for patient application.
3. Visually inspect packaging label. Check expiration date and time. Adhere strictly to expiration date and time guidelines.

9. DIRECTIONS FOR USE

A. Method of Application

1. Prepare the wound bed so that it is clean and hemostasis has been maintained.
2. Open outer clear chevron package of the OrCel™ device containing the plastic tray enclosed in an inner sterile pouch.
3. Dispense inner sterile pouch containing plastic tray onto the sterile field.
4. Open the sterile pouch and place the tray on a sterile flat surface with the blue mesh backing dermal side facing up.
5. To open the tray, stabilize the bottom tab while simultaneously lifting up on the top tab.
6. Using sterile non-crushing forceps, gently remove and **discard** the blue mesh backing material.
7. With two sterile non-crushing forceps, grasp adjacent corners of the device in unison with the white mesh backing material.
8. Position the device so that the white mesh backing material (covering the epidermal surface) is facing up and away from the cleaned wound bed. Leave white mesh in place to serve as the primary **cover** layer for OrCel™.
9. In this orientation, the dermal aspect of the device is in direct contact with the wound bed.
10. The OrCel™ device should be positioned so that there is a slight overlap (approximately 0.5 cm) onto intact skin. If more than one device is used to cover a wound surface, a slight overlapping of the edges of each OrCel™ device is recommended. Once placed on the wound bed, further manipulation of the OrCel™ device to improve positioning should be minimized, although it may be performed, as long as the device is grasped together with the white backing in place and moved in unison.
11. Cover the OrCel™ device(s) with a non-adherent dressing and outer gauze wrap.
12. Allow overlying dressings to remain undisturbed for approximately 48 to 72 hours and then follow post application directions for care.

B. Post Application Directions of Care

1. After OrCel™ has been applied to the affected areas as instructed in the directions for use, the donor site should be inspected by removing overlying non-adherent dressings at a minimum of every 48 to 72 hours.

   Note: The white mesh backing lying directly on top of the OrCel™ should remain in place for 1 week.

2. The site should be inspected for any signs of redness, tenderness, itching, pain, or foul odor. If present, treat according to standard clinical practice. The surrounding area may be gently cleansed with normal saline.

3. The site should be redressed with non-adherent dressings and an overlying gauze wrap.

4. After 1 week, the dressings should be removed and an attempt to gently peel back the white backing with forceps should be made.

   NOTE: The white backing may be adherent and may require soaking the area with normal saline to encourage loosening of the backing material. If portions of the backing remain adherent despite soaking, leave in place for approximately 24 to 48 hours and reattempt.

   Because OrCel™ does not persist on the wound surface, it may not be present visibly when the white backing is removed.

5. Once the white backing has been completely removed, gently cleanse the area with normal saline. If there are portions of the wound that remain unhealed, cover with non-adherent dressings and wrap with an overlying gauze wrap. Continue to assess healing of the area on a 24- to 48-hour basis.

6. Once the area has healed, caution should be taken to prevent any unnecessary trauma to the newly healed area, as newly healed skin may be fragile and susceptible to wound breakdown. Patients are instructed to care for the newly healed skin as directed by their physicians.

7. Patients **should be** instructed to inspect the newly healed area daily for any of the following signs of breakdown: redness, tenderness, blistering, foul odor, drainage, or a moist, glistening appearance of the area. If any of these signs appear, the patient should notify their physician.

8. Patients **should be** instructed not to rub any creams, lotions or medicines into the treated area unless directed by their physician.

10. PATIENT INFORMATION

Patients and parents should be counseled regarding the following information:

1. Basic information about patient's condition,

2. Basic information about OrCel™,

3. How OrCel™ is used in the treatment of donor sites, and

4. Post-operative care.

11. PEEL OFF LABEL

Remove the peel-off label from the OrCel™ package label and place it in the patient's chart. This label bears the lot number and expiration date of the OrCel™.

Manufactured By: Ortec International, Inc.
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Date of Issuance: Month XX, 200X [insert date of approved labeling]